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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/690,800	10/21/2003	Edmond J. LaVoie	735.038US2	5628

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EXAMINER	
MITCHELL, GREGORY W	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 06/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/690,800	LAVOIE ET AL.	
	Examiner	Art Unit	
	Gregory W Mitchell	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-28 are pending.

Priority

This application is a divisional application of US 09/869141, filed on June 13, 2001, entitled "Heterocyclic Topoisomerase Poisons," which is a continuation of PCT/US98/27822, entitled "Heterocyclic Topoisomerase Poisons," filed on December 30, 1998, which claims priority to U.S Provisional Application 60/070287, filed on December 31, 1997, entitled "Heterocyclic Topoisomerase Poisons." Applicant's priority is acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-28 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of human T cell acute lymphoblastic leukemia utilizing some compounds, does not reasonably provide enablement for the treatment of all cancers utilizing all compounds within the scope of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The specification does not provide sufficient information that all cancers are treatable by all bis-benzimidazoles described in the methods claimed.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547, the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1). ***The Nature of the Invention***:

All of the rejected claims are drawn to an invention which pertains to a method of treating mammals with variously substituted bisimidazoles for the inhibition of cancer cells. The nature of the invention is complex in that it encompases the treatment of all types of cancers with a wide array of variously substituted bisimidazole compounds.

(2). ***Breadth of the Claims***:

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass inhibition of any number of cancers by a bisimidazole to be administered in any concentration. What's more, the scope of the compounds claimed to be useful for the inhibition of cancer cells is extremely broad. There are countless

possibile compounds for the treatment claimed due to the breadth of the substituents: R_1, R_2, R_3, R_4 and R_5.

(3). ***Guidance of the Specification***:

The guidance given by the specification as to how one would administer the claimed compounds to a subject in order to inhibit any type of cancer cell is limited. All of the guidance provided by the specification is directed toward the treatment of specific cancers (RPMI, lymphoblastic leukemia, and CPT-K5, RPMI's camptothecin-resistent variant cell line) with one of four specific compounds. What's more, the cytotoxicity of the different compounds were observed to vary by 30 fold, providing little guidance for the expectation of other compounds within the scope of Applicant's claimed invention. For example, a marked difference in cytotoxicity is observed between compounds 2 , 3 and 5 and compound 4. Furthermore, compound 4 does not even exhibit any activity as a topoisomerase I poison. Applicant attributes these difference to the fact that compound 4 does not possess an N-H group whereas compounds 2, 3 and 5 do possess such a group. The question arises, however, as to what activity a compound would possess if the lone pair of the N-H group was sp^3 hybridized rather than conjugated as are the lone pairs of compounds 2, 3 and 5. Furthermore, the cytotoxicity of compounds 2 and 3 versus CPT-K5 vary significantly (50 fold) despite the fact that both possess an N-H with conjugated nitrogens. Finally, a hydrogen salt of compound 4 would fall within the scope of the compounds claimed to be useful for inhibiting cancer cells but Applicant does not provide any evidence that the salt would be any more effective at inhibiting

cancer cells than would the neutral form of compound 4. Accordingly, because of the significant variation in the cytotoxicity of the compounds, the illustration of dosage forms in Example 4 of Applicant's specification would not be expected by one of ordinary skill in the art to be applicable to all claimed compounds.

Furthermore, the dosages described in Applicant's specification are completely generic as to disorder – the dosages are not only given without reference to the compound utilized but also without reference to the disease treated.

(4). ***Working Examples***:

Applicant provides *in vitro* examples of the cytotoxicity of compounds 2 and 3 of Figure 1 versus RPMI, lymphoblastic leukemia, and its camptothecin-resistent variant cell line CPT-K5. Applicant also provides cytotoxicity measurements of two unclaimed compounds.

(5). ***State of the Art***:

While the state of the art is relatively high with regard to treating specific cancers, the state of the art with regard to treating cancer generally is underdeveloped. In particular, there is no known anticancer agent which is effective against all cancers. Carter, et al. (*Chemotherapy of Cancer*, 2nd ed., 1981) clearly teaches that for the forty known anticancer agents, none are effective against all cancers (pages 362-365). There are compounds that treat a range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present

understanding in oncology. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Even those that affect a single organ are often not generally treatable. For example, the main types of lung cancer are small cell (oat cell), giant cell, clear cell, adenocarcinoma of the lung, squamous cell cancer of the lung, and mesothelioma. There is no such thing as a treatment of these generally because of their diversity. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task.

(6). ***Predictability of the Art***:

The invention is directed to inhibiting cancer cells in general. It is well established that "the scope of enablement various inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839 (1970). Cancers are especially unpredictable due to their complex nature. Please refer to the discussion of Carter, et al. and the state of the art in (5) that shows the different treatments of cancers. The treatment of one type of cancer could not be necessarily the same for the other type.

(7). ***The Quantity of Experimentation Necessary***:

In order to practice the claimed invention, one of skill in the art would have to first envision a combination of an appropriate pharmaceutical carrier, a dosage for each compound, the duration of treatment, route of treatment, etc. and, in the case of human treatment, an appropriate animal model system for one of the claimed compounds. One would then need to test the combination in the model system to determine whether or not the combination is effective for inhibiting cancer cells. If unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regarding treatment of cancer with any compound, one of skill in the art would have to then either envision a modification of the first combination of pharmaceutical compound, compound dosage, duration of treatment, route of adminstration, etc. and appropriate animal model system, or envision an entirely new combination of the above and test the system again. If again unsucessful, which is likely given the lack of significant guidance from the specification or prior art regarding treatment of cancer with any compound, the entire, unpredictable process would have to be repeated until successful. In order to practice Applicant's invention, it would be necessary for one to conduct the preceding experimentation for each type of cancer because, as described by Carter, et al., there is no known drug effective for inhibiting all types of cancer. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to inhibit cancer cells in a mammal by administration of one of the compounds within the claims.

Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and

"[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, a method for inhibiting cancer cells generally by administering the various bis-benzimidazole compounds of the claims is not considered to be enabled by the instant specification.

Double Patenting

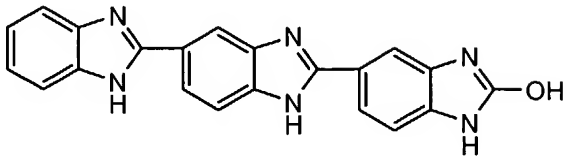
The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

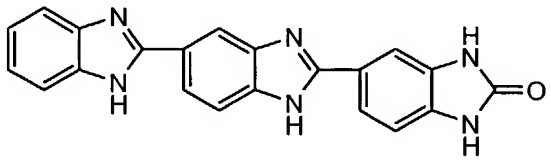
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-7, 10, 12-21 and 26-28 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,221,892. Although the conflicting claims are not identical, they are not patentably distinct from each other because if, for example, R_1-R_7 of the terbenzimidazole in claim 1 of U.S. Patent No. 6,221,892 are all hydrogen

and R_8 is hydroxyl, the following compound is claimed in a method for treating cancer:



In the current application, Applicant is claiming a method for treating cancer utilizing a compound wherein, for example, R_1-R_3 are all hydrogen and R_4 and R_5 taken together are –NH-(C=O)-NH-, giving the following structure:



The ene-ol of U.S. Patent No. 6,221,892 renders the carbonyl of the currently claimed invention obvious because it is well known in the art that an ene-ol can tautomerize to the ketone. Accordingly, this double patenting rejection is deemed proper.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory W Mitchell whose telephone number is 571-272-2907. The examiner can normally be reached on M-F, 8 AM - 4 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gregory W Mitchell
Examiner
Art Unit 1617

gwm

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER